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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/103,745	06/24/1998	SUDHIR AGRAWAL	475.08.642CI	3401

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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/103,745	Applicant(s) AGRAWAL, SUDHIR	
	Examiner J. Douglas Schultz	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/09/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

FILE

DETAILED ACTION

Priority

As noted in the previous Office action, it is noted that this application discloses and claims subject matter disclosed in prior Application No. 08/711,568, now U.S. Patent Number 5,856,462, and names an inventor or inventors named in the prior application. Accordingly, this application may constitute a continuation CIP, or division. Should Applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78. If Applicant intends to name continuing or CIP status of said parent in the instant application, Applicants are required to amend the first line of the specification to indicate the relation to said parent and to update the status of the application as the issued patent. CIP status requires naming the application in the oath under section 120 along with a" duty to disclose" clause as per section 120. CORRECTION IS REQUIRED. Note that such continuing data should include the relation of the PCT application named in the transmittal papers filed on 6/24/98.

Double Patenting

It is acknowledged that Applicant's response to the double patenting rejection of Sept. 9, 1999 indicated that, should any pending claims be indicated as allowable, Applicant will file a Terminal Disclaimer disclaiming the portion of the term of the patent beyond the expiration date of U.S. Patent Number 5,856,462.

Response to Arguments

Applicant's response filed October 9, 2002 has been considered. Rejections and/or objections not reiterated from the previous office action mailed September 9, 2002 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Claim 1 stands rejected under 35 U.S.C. 102(a) as being anticipated by Krieg et al. (WO/9602555A1 or Antisense or Nucleic Acid Drug Development), or by Zhao et al., for the same reasons of record as set forth in the Office action of September 9, 1999.

Krieg et al. and Zhao et al. teach phosphorothioate oligonucleotides containing CpG motifs, wherein said oligos may contain alkylphosphonate, 2'-substituted, stereospecific phosphotothioate, phosphotriester, inverted, phosphoroamidate, or 2'-5' modifications.

Despite Applicant's amendment, the claims as written are still broad enough to encompass the cited prior art. For example, in light of the specifications definition of an inverted CpG as being simply a GpC, all the above references teach an inverted modified phosphorothioate CpG motif.

Claims 3 and 4, stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of using the contemplated compounds in cell

culture, does not reasonably provide enablement for methods of treating mammals or methods of therapy using the instantly contemplated compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims, for the same reasons of record as set forth in the Office action of September 9, 1999. Furthermore, new claim 5 is rejected for the same reasons as claims 3 and 4; response to Applicant's arguments and elaboration on the reasons for lack of enablement are outlined below.

Applicant argues that one of ordinary skill would not have to engage in undue experimentation to identify effective antisense oligonucleotides. Applicant also argues that, according to the M.P.E.P., the *in vitro* model provided constitutes a working model, because the *in vitro* model correlates with the *in vivo* aspect of the invention as claimed. Applicant also argues that the prior art is predictable enough to support enablement; in support, Applicant has provided the reference of Milner et al., which discloses a high throughput screen to identify effective antisense inhibitors. Further, Applicant has provided a discussion of Monia et al., and of Galderisi et al. that demonstrate examples of successful antisense therapy. Several other articles are discussed that demonstrate the promise of antisense therapy in the whole animal models.

Applicant's arguments have been fully considered but they are not persuasive. The state of the art of using oligonucleotide compounds for *in vivo* therapy remains highly unpredictable. Furthermore, the specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in

in vivo environments. A person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable.

While some successes have been observed, as evidenced in Applicant's submission of prior art, the large preponderance of evidence regarding the successful use of oligos in antisense mediated treatment demonstrates that major obstacles that persist in the art, as outlined in a recent (2002) article by Braasch et al.: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal

structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch

affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

Thus, the prior art as a whole underscores the unpredictability of translating success *in vitro* to success *in vivo*, particularly in relation to predicting oligo interactions with systemic and cellular proteins, or the generation of maladaptive immune responses, or to the identification of and delivery to the appropriate target sites in the whole animal.

Moreover, one skilled in the art would not accept on its face the *in vitro* examples given in the specification as being correlative or representative of the successful *in vivo* use of antisense compounds or treatment of any and/or all conditions or diseases as claimed. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or disease

suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

Said claims are drawn very broadly to compounds and methods of treating any condition or disease caused by aberrant gene expression in humans. The quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with low toxicity and immunogenicity that are successfully delivered, and most importantly, that target sites in appropriate cells and /or tissues harboring ab expression such that all harmful expression is inhibited, that healthy expression is permitted appropriately *in vivo,* and further, that treatment and/or preventive effects are provided for any and/or all diseases or conditions suspected of being associated with aberrant gene expression *in vivo*. Since the specification fails to provide any guidance for the successful treatment or prevention of any and/or all diseases or conditions suspected of being associated with aberrant gene expression in humans, or their tissues or cells, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation as presented in the specification over the scope claimed.

Regarding Applicant's references in considering the state of the art as a whole as required by *in re Wands,* it is noted that Applicants' submission of articles consists mostly of primary references, each of which describe the results of only one series of experiments; such primary

research articles don't presume to indicate the state of the art as a whole. In contrast, the articles submitted by the examiner are all review papers, whose function it is to distill a large volume of primary literature, such as those submitted by Applicant, and then to discuss and analyze problems, successes, trends and future directions. The focus of such review articles is most appropriate in providing a comprehensive analysis of the state of *in vivo* anti-sense mediated gene inhibition. It is not argued that there have been irregular incidences of success in using antisense *in vivo*; however, when the primary literature supplied by Applicant is put in the context of the art as a whole, as has been done in the review articles cited above, it is clear that such primary references supplied by Applicant do not indicate that the state of the art of providing treatment and prevention of disease using antisense compounds and methods as claimed is at all predictable, and thus enabled.

Finally, Applicant argues that the *in vitro* models provided correlate with *in vivo* studies and therefore constitute a working model. This view is not adopted. While Applicant asserts that the *in vitro* example is a model of *in vivo* activity, it is reiterated that the primary reasons for lack of enablement of such treatment *in vivo* is due to problems with non-specific interactions of administered oligos with plasma and/or cellular proteins that it encounters before contacting its target, and to significant immune reactions to said administration, and finally to problems with target access itself, that is entering the cell and binding to the transcript so that inhibition occurs. The *in vitro* model does not allow for testing or resolution of these issues, and as such cannot provide proper guidance in these areas, let alone determine if treatment or prevention associated with the claimed inhibition of that protein would ever be observed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
November 18, 2002

ANDREW WANG
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